Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state

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SUMMARY Several studies have shown symptomatic and haemodynamic improvement after the introduction of angiotensin converting enzyme inhibitors in patients with heart failure treated with diuretics. The concomitant long term effects of the new orally effective long acting angiotensin converting enzyme inhibitor, enalapril, on symptoms, exercise performanc, cardiac function, arrhythmias, hormones, electrolytes, body composition, and renal function have been further assessed in a placebo controlled double blind cross over trial with treatment periods of eight weeks. Twenty patients with New York Heart Association functional class II to IV heart failure who were clinically stable on digoxin and diuretic therapy were studied. Apart from the introduction of enalapril, regular treatment was not changed over the study period; no order or period effects were noted. Enalapril treatment significantly improved functional class, symptom score for breathlessness, and exercise tolerance. Systolic blood pressure was significantly lower on enalapril treatment. Echocardiographic assessment indicated a reduction in left ventricular dimensions and an improvement in systolic time intervals. In response to enalapril, the plasma concentration of angiotensin II was reduced and that of active renin rose; plasma concentrations of aldosterone, vasopressin, and noradrenaline fell. There were signficant increases in serum potassium and serum magnesium on enalapril. Glomerular filtration rate measured both by isotopic techniques and by creatinine clearance declined on enalapril while serum urea and creatinine rose and effective renal plasma flow increased. Body weight and total body sodium were unchanged indicating that there was no overall diuresis. There was a statistically insignificant rise in total body potassium, though the increase was related directly to pretreatment plasma renin ($r = 0.5$). On enalapril the improvement in symptoms, exercise performance, fall in plasma noradrenaline, and rise in serum potassium coincided with a decline in the frequency of ventricular extrasystoles recorded during ambulatory monitoring. Adverse effects were few.

In patients with heart failure, enalapril had a beneficial effect on symptoms and functional capacity. The decline in glomerular filtration rate on enalapril may not be beneficial in early heart failure.

The three principal groups of drugs used to treat heart failure are diuretics, digitalis preparations, and

vasodilators. Whereas the place of diuretics is firmly established, the value of digitalis in the long term treatment of heart failure with sinus rhythm remains controversial[1][2] and the results of controlled trials of vasodilators are conflicting.[3-6]

Angiotensin converting enzyme inhibitors should have all the advantages of conventional vasodilators

in the treatment of cardiac failure together with several substantial additional benefits. Angiotensin II is an important stimulus to aldosterone secretion[7]; and lowering plasma angiotensin II by angiotensin converting enzyme inhibition should reduce aldosterone secretion and thus facilitate diuresis while also correcting any deficiency of potassium and magnesium associated with diuretic therapy and aldosterone excess.[8][9]

Hyperaldosteronism is particularly likely to occur with prolonged diuretic treatment of heart failure and the resulting electrolyte abnormalities predispose patients to cardiac arrhythmias.[10][11]

The high circulating concentrations of angiotensin II encountered in heart failure can stimulate excessive secretion of vasopressin[12] which hinders diuresis.[13] Reduction of vasopressin secretion by angiotensin converting enzyme inhibition should promote fluid excretion. Angiotensin II also stimulates the sympathetic nervous system at various sites[14] and inhibits vagal transmission[15]; angiotensin converting enzyme inhibition will reverse these actions.[16][17] Angiotensin II also has direct renal actions in cardiac failure. Despite a profound reduction in renal blood flow,[18] glomerular filtration rate and urea excretion[18][19] are well preserved until a late stage of heart failure. This maintenance of renal function is mainly the result of the intrarenal actions of angiotensin II which increases efferent glomerular arterial tone[20] and enhances the efficiency of vasa recta countercurrent exchange mechanisms.[19] In

late cardiac failure, however, excessive intrarenal angiotensin II can cause glomerular shutdown with rapidly advancing uraemia and hyponatraemia.[19] Thus angiotensin converting enzyme inhibition might benefit the kidney in advanced heart failure, but at earlier stages might worsen some aspects of renal function.

Several well controlled trials of angiotensin converting enzyme inhibition in cardiac failure have now shown clinical benefit,[21–25] although, to our knowledge, only one using captopril has concurrently evaluated symptoms together with metabolic, hormonal, and renal changes.[26]

We report here the effects of enalapril, a new long acting angiotensin converting enzyme inhibitor, determined in 20 patients with heart failure in a trial with a double blind cross over design for within patient comparisons. In addition to assessing symptoms and exercise performance we measured renal function, serum and total body electrolytes, the renin-angiotensin system, and plasma aldosterone, vasopressin, and catecholamine concentration.

Patients and methods

PATIENT SELECTION
We studied 20 patients with chronic heart failure caused by ischaemic heart disease (nine), congestive (dilated) cardiomyopathy (eight), or severe left ventricular dysfunction after successful valve replacement (three) who were in New York Heart Associ-

Table 1 *Biochemical variables measured at baseline, during enalapril treatment, and during placebo treatment*

		Baseline	Enalapril	Placebo	Significance*
Serum sodium (mmol/l) (n = 19)		139 (4)	138 (4)	139 (3)	NS
Serum potassium (mmol/l) (n = 19)		3·8 (0·3)	4·2 (0·3)	3·7 (0·3)	p < 0·00001
Serum magnesium (mmol/l) (n = 19)		0·755 (0·183)	0·835 (0·081)	0·817 (0·080)	p < 0·05
Serum urea (mmol/l) (n = 19)		6·4 (2·0)	8·0 (2·4)	6·4 (1·9)	p < 0·001
Serum creatinine (μmol/l) (n = 19)		100 (24)	110 (31)	101 (24)	p < 0·01
Total body sodium (mmol) (n = 16)		3385 (621)	3267 (512)	3390 (575)	NS
Total body potassium (mmol) (n = 16)		2659 (619)	2787 (635)	2741 (669)	NS
Plasma active renin:					
(μU/ml) (n = 19)	Mean	81	695	98	
	Median	47	406	61	
	Range	3–532	3–2256	3–673	p < 0·00001
Plasma angiotensin II (pmol/l):					
(n = 18)	Mean	39	14	34	
	Median	31	13	29	
	Range	1–160	4–35	1–83	p < 0·005
Plasma aldosterone (ng/dl):					
(n = 19)	Mean	14	10	16	
	Median	10	8	9	
	Range	6–37	4–39	3–85	p < 0·05
Plasma noradrenaline (nmol/l) (n = 16)		3·2 (1·4)	2·2 (0·8)	3·2 (1·2)	p < 0·002
Plasma adrenaline (nmol/l) (n = 16)		0·3 (0·1)	0·3 (0·2)	0·4 (0·2)	NS
Plasma vasopressin (pg/ml):					
(n = 18)	Mean	1·9	1·3	2·2	
	Median	1·6	1·1	1·5	
	Range	0·3–5·1	0·2–3·6	0·5–7·8	p < 0·02

*Statistical significance of difference between enalapril and placebo. Values are mean (SD) unless otherwise stated.

Conversion: traditional units to SI—Aldosterone: 36·1 ng/dl = 1000 pmol/l. Vasopressin: 1 pg/ml = 0·923 pmol/l.

ation class II or IV. Mean (SD) duration of symptoms at entry was 18 (13) months. All had had symptoms for more than three months. Patients with serious concomitant disease or appreciable valvar regurgitation were excluded. All vasodilators were withdrawn at least one month before investigation and doses of frusemide (mean (SD) daily dose 124 (57) mg/day) and digoxin (mean daily dose 0·22 (0·06 mg/day) were held constant. One patient refused frusemide and continued on bumetanide 3 mg/day. Four patients were also on amiloride 10–15 mg/day, five on potassium chloride (1·8–2·4 g/day), one on hydrochlorothiazide 100 mg/day, and one had been treated with amiodarone 400 mg/day for the previous two years; doses of these agents were also held constant through the trial.

STUDY DESIGN

Patients were assessed and were familiarised with study procedures including repeated exercise tests four weeks before the start of the study. They were then admitted for 10 days for full initial assessment before being randomly allocated to enalapril 5 mg/day or matching placebo. Doses of enalapril (or matching placebo) were then doubled every two weeks to a maximum of 40 mg once daily (9 am) if no adverse effect occurred. After two months patients were readmitted, reassessed, and then they were started on the alternative treatment. Doses were again doubled every two weeks and patients were finally assessed after a further two months in the trial.

METHODS

Symptoms were evaluated by New York Heart Association score and by visual analogue scores for breathlessness, tiredness, and ankle swelling. Exercise capacity was measured by a modified Bruce protocol with stages which lasted three minutes. Left ventricular internal dimensions were derived from M mode echocardiography[27] and systolic time intervals from the aortic root echocardiogram.[28] Ambulatory electrocardiographic monitoring was performed for 48 hours with a Medilog-1 system and the results were expressed as events per 24 hours. Repetitive extrasystoles were defined as three or more consecutive ventricular extrasystoles. Blood pressure was measured with a Hawkesly random zero sphygmomanometer and heart rate was taken from the apex beat six hours after dosing.

Venous blood was drawn at 9 am, 24 hours after dosing from the patients who had fasted (apart from water), and remained supine overnight. Samples were assayed for serum electrolyte, urea, and creatinine concentrations, and for plasma concentrations of active renin[29] (normal range 10–50 μU/ml), angiotensin II[30] (normal range 5–35

pmol/l), aldosterone[31] (normal range 4–18 ng/dl (150–500 pmol/l)), vasopressin[32] (normal range 0·3–0·7 pg/ml (0·3–0·6 pmol/l)), noradrenaline (normal range 0·8–3 nmol/l), and adrenaline (undetectable—0·2 nmol/l).[33]

Total body potassium was derived from endogenous ^{40}K[34] by means of a whole body counter, and total body sodium was similarly determined after neutron activation.[35–37] Effective renal plasma flow[38] and glomerular filtration rates[39] were determined by single injection isotope techniques. Creatinine clearance was calculated from 24 hour urine collection and serum creatinine.

STATISTICAL ANALYSIS

Possible order and period effects or both were assessed by comparison of the differences between observations for the enalapril and placebo phases for the two groups by means of two sample t tests. In cases where the order effect was not significant we compared treatment effects by means of paired t tests on the enalapril and placebo measurements and ignored the order of treatment. Correlations were calculated by Pearson's product moment correlation coefficient and these were tested for significance by t tests. The data were log transformed where appropriate.

Results

In 17 patients the dose of enalapril was increased to a maximum of 40 mg/day, in two patients the dose was limited to 20 mg/day, and in one to 10 mg/day because of symptomatic hypotension, which also occurred in two patients on 40 mg/day. No severe hypotension was observed after the first dose in any patient. No patient failed to reach the maximum dose of placebo. Nineteen patients completed the study; one patient died suddenly during the placebo phase after showing an improvement in symptoms and exercise capacity on enalapril.
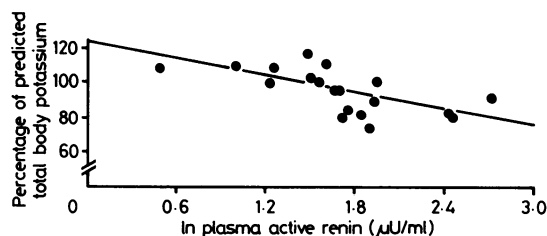

Fig *Relation between total body potassium (expressed as a percentage of predicted normal) and log (ln) plasma active renin concentration (r = −0·61; p < 0·01).*

BIOCHEMICAL VARIABLES

Hormone assays
At baseline and on placebo, mean plasma concentrations of active renin and angiotensin II were higher than normal but there was wide variation (Table 1). Plasma angiotensin II concentrations remained suppressed for 24 hours after the last dose of enalapril and there was a concomitant rise in plasma active renin concentration.

At baseline and during the placebo phase mean plasma concentrations of aldosterone, noradrenaline, and adrenaline were at the upper limit of normal and plasma vasopressin was raised; again values varied widely. Plasma concentrations of all these hormones, except adrenaline, fell during treatment with enalapril.

Electrolytes
At baseline and on placebo, mean serum potassium and magnesium were at the lower limit of normal and total body potassium was low at 96(13)% (mean (SD)) of predicted normal values. There was a significant increase in serum potassium and magnesium on enalapril. Total body potassium increased and total body sodium decreased, though neither change was statistically significant. There was no overall change in serum sodium. In two patients in whom postural hypotension developed (standing blood pressure on placebo 96/66 mm Hg and 108/88 mm Hg falling to 72/56 mm Hg and 68/44 mm Hg respectively on enalapril) serum sodium was reduced

on enalapril (from 139 to 134 mmol/l and from 134 to 121 mmol/l respectively). In two other patients, however, serum sodium rose on enalapril (from 129 to 133 mmol/l and from 134 to 137 mmol/l).

Total body potassium was negatively correlated with plasma active renin concentration measured at baseline ($r = -0.61$; $p < 0.01$) (Fig.). Changes in total body potassium ($r = 0.5$) and in total body sodium ($r = -0.21$) with enalapril were both related to initial plasma renin concentration though only the rise in total body potassium was statistically significantly related ($p < 0.05$).

Before treatment with enalapril plasma concentrations of the following hormones correlated significantly with plasma angiotensin II; active renin ($r = 0.90$; $p < 0.001$), aldosterone ($r = 0.57$; $p < 0.01$), vasopressin ($r = 0.49$; $p < 0.05$), and noradrenaline ($r = 0.66$; $p < 0.002$).

CLINICAL VARIABLES

Blood pressure and heart rate
Both systolic and diastolic blood pressure were significantly reduced on enalapril and heart rate also declined (Table 2).

Left ventricular function
Echocardiographic left ventricular systolic and diastolic dimensions were reduced by enalapril, although fractional shortening did not increase significantly (Table 2). The ratio of pre-ejection period to left ventricular ejection time was also

Table 2 *Clinical variables measured at baseline, during enalapril treatment, and placebo treatment*

		Baseline	Enalapril	Placebo	Significance*
Breathlessness (mm) (n = 19) mean (range)		56 (15–92)	24 (0–89)	45 (3–95)	
median		61	7	45	p < 0·006
Tiredness (mm) (n = 19) mean (range)		51 (0–100)	29 (0–88)	39 (0–96)	
median		58	13	41	NS
Systolic blood pressure (mm Hg) (n = 19)		117 (22)	100 (23)	121 (24)	p < 0·00001
Diastolic blood pressure (mm Hg) (n = 19)		75 (12)	62 (11)	72 (10)	p < 0·001
Heart rate (beats/min) (n = 18)		79 (12)	72 (9)	76 (10)	p < 0·03
Weight (kg) (n = 19)		66 (11)	67 (11)	67 (11)	NS
Glomerular filtration rate (ml/min) (n = 18)		70 (25)	58 (23)	71 (23)	p < 0·00001
Creatinine clearance (ml/min) (n = 17)		69 (29)	65 (24)	72 (23)	p < 0·04
Effective renal plasma flow (ml/min) (n = 15)		289 (101)	354 (128)	308 (119)	p < 0·008
Exercise time (min) (n = 19)		6·5 (3·2)	10·7 (2·4)	8·7 (3·1)	p < 0·01
LVEDD (cm) (n = 18)		6·9 (1·0)	6·6 (0·9)	6·9 (0·9)	p < 0·004
LVESD (cm) (n = 18)		5·8 (1·2)	5·4 (1·0)	5·8 (1·2)	p < 0·003
Fractional shortening (n = 18)		16 (7)	18 (7)	17 (6)	NS
PEP : LVET (n = 16)		667 (204)	534 (186)	631 (172)	p < 0·03
Ventricular extrasystoles:					
(per 24 h) (n = 19)	Mean	1702	1268	2140	
	Median	555	560	659	
	Range	15–11045	17–7827	17–9130	
Repetitive ventricular extrasystoles:					
(per 24 h) (n = 19)	Mean	4·6	3·9	4·7	
	Median	1	1·5	1	
	Range	0–41	0–35	0–58	

*Statistical significance of difference between enalapril and placebo. Values are mean (SD) unless otherwise stated. LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; PEP : LVET, ratio of pre-ejection period to left ventricular ejection time.

reduced, indicating an improvement in ventricular function.

Ambulatory monitoring

Ventricular extrasystoles were significantly reduced (by 50%) during enalapril treatment, but the reduction in repetitive extrasystoles was not statistically significant.

Renal function

During enalapril treatment glomerular filtration rate measured isotopically was reduced and creatinine clearance also fell significantly, whereas effective renal plasma flow increased. The decline in glomerular filtration rate was reflected in a rise in serum urea and creatinine.

Exercise testing

Exercise performance improved on average by one treadmill stage during enalapril treatment.

Symptoms

New York Heart Association score improved (Table 3) during treatment with enalapril. Breathlessness and tiredness also improved but ankle swelling, not a prominent complaint at the start of the study, was unchanged.

ADVERSE EFFECTS

Weight increased in the first week on enalapril ($0.4(0.8)$ kg; $p < 0.05$) whereas there was no change after one week on placebo ($-0.1(0.6)$ kg). One patient had weight gain with increased ankle swelling; the latter improved on continued therapy without alteration of diuretic dose. Weight was similar on placebo and enalapril at the end of both two month periods.

Adverse responses included hypokalaemia (serum potassium < 3.5 mmol/l) in eight patients on placebo; slight increases in transaminases, one patient on placebo (alanine transaminase 62 U/l) and one on enalapril (60 U/l); and a pronounced increase in serum urea (6.8 mmol/l to 12.0 mmol/l) and creatinine (127 µmol/l to 202 µmol/l) in one patient on enalapril who also had postural hypotension (standing blood pressure on placebo 98/74 mm Hg and on enalapril 66/54 mm Hg). No patient developed proteinuria or a blood dyscrasia.

Other possible adverse effects were a mild persistent dry cough in one patient on enalapril. Transient skin eruptions were noted in three patients on enalapril (one case each of varicose eczema and two cases of a macular rash of hands or feet) and two on placebo (one case of varicose eczema and one of urticaria). In addition one patient developed thoracic herpes zoster during enalapril therapy from which

Table 3 *New York Heart Association functional class at baseline, after treatment with enalapril, and on placebo. The difference between placebo and enalapril treatments was significant ($p < 0.05$) by a modified χ^2 test*

Class	Baseline	Enalapril	Placebo*
4	2	0	2
3	14	3	9
2	4	15	8
1	0	2	0
Mean score	2·9	2·1	2·7

*One death.

she made an uncomplicated recovery. One patient who had previously had raised fasting blood glucose (8 mmol/l at baseline) developed glycosuria and a further increase in his fasting blood glucose on enalapril (placebo 11·9 mmol/l, enalapril 13·4 mmol/l) which he had received after placebo.

Discussion

The present trial has confirmed earlier reports of beneficial effects on exercise time and dyspnoea in patients with heart failure treated with the angiotensin converting enzyme inhibitors captopril[21-26] and enalapril. The degree of improvement in exercise performance was similar to that observed in other studies of enalapril but the placebo response in our study was also much greater than that reported in other studies.[24 25]

Our study design precludes any effect of patient training, allows within patient comparison of drug and placebo responses, and avoids difficulties in matching the baseline characteristics in placebo and active treatment groups which have affected other studies.[24] We saw no evidence of an order effect, indicating that the double blind treatment periods were long enough to exclude a carry over effect into placebo period, which would tend to cause drug action to be underestimated. Unlike the other two reported studies of enalapril regular diuretic therapy was unchanged in our patients.[24 25]

A single daily dose of enalapril was sufficient to sustain a reduction in angiotensin II and an increase in active renin over 24 hours. Mean plasma aldosterone, noradrenaline, and vasopressin concentrations were raised before angiotensin converting enzyme inhibition, and correlated significantly with angiotensin II concentration. When angiotensin II formation was inhibited concentrations of all of these hormones fell. This could have been the result of clinical improvement, but a reduction of the reported stimulatory effect of angiotensin II on sympathetic neuronal activity and on the secretion of vasopressin and aldosterone[7] is more likely. A decrease in plasma noradrenaline has already been reported after both short[16 40] and long term[16 26] angiotensin converting enzyme inhibition in patients

with heart failure. We do not know of other reports of evidence of suppression of vasopressin secretion although such an effect is likely. Controlled studies of angiotensin converting enzyme inhibition in heart failure have consistently demonstrated long term suppression of plasma aldosterone[26 41 42] perhaps caused by the counter regulatory effect of increased serum potassium concentration.[43] A fall of plasma aldosterone could be important in maintaining sodium balance as blood pressure and glomerular filtration rate fall. Reduction in sympathetic activity and of plasma vasopressin concentrations may result in additional arterial and venous dilatation[43 44]; the latter is likely to promote excretion of water.[13]

We found that serum potassium and magnesium concentrations rose on enalapril, and this effect may have been largely a result of a related fall in plasma aldosterone. In contrast to our earlier study with captopril,[26] the rise in mean total body potassium on enalapril was not statistically significant. The increase of body potassium on enalapril was directly related to the baseline plasma renin. Moreover, the extent of initial potassium depletion is related to plasma renin.[45] Thus increases in total body potassium with angiotensin converting enzyme inhibition might be expected only in patients who are already potassium depleted. Transient weight gain, which we have also observed with captopril,[26] occurred in the first week of enalapril therapy. This was probably largely due to a fall in blood pressure and possible renal dysfunction.[46] In the long term weight was unchanged, suggesting that there may have been a secondary diuresis probably aided by the falls in plasma aldosterone and vasopressin. We observed no long term changes in mean serum sodium or total body sodium. There was a significant reduction in ventricular extrasystoles during enalapril treatment, probably partly reflecting the increases in serum potassium and magnesium, the reduction in sympathetic activity, and the reduced cardiac dimensions. Several studies have shown that frequent ventricular extrasystoles indicate a poor prognosis in heart failure,[47 48] and sudden death, presumably from arrhythmias, is common in patients with left ventricular failure.[49] If a causal relation does exist this is one mechanism whereby angiotensin converting enzyme inhibitors might reduce mortality.

As we had expected on theoretical grounds[20] and from earlier experience[26] enalapril treatment, although it increased renal blood flow, led to a fall in both creatinine clearance and in glomerular filtration rate measured isotopically and an increase in serum urea and creatinine concentrations. These changes represent the loss of a beneficial direct intrarenal action of angiotensin II. In cardiac failure enhanced angiotensin II mediated constriction of the efferent glomerular arterioles[18 20] probably helps to sustain glomerular filtration. Blood is also diverted to the large juxtamedullary glomeruli which have long loops of Henle that descend deep into the renal medulla accompanied by vasa recta.[50 51] Angiotensin II mediated increased tone in the vasa recta may improve counter current exchange in the renal medulla and thus sustain urea excretion.[19] Reduction of intrarenal angiotension II by angiotensin converting enzyme inhibition would lead to loss of these various compensatory effects and thus to a fall in glomerular filtration rate and a rise in serum urea concentration. Only in very severe cardiac failure, in which gross excess of intrarenal angiotensin II causes preglomerular arteriolar constriction,[19 52 53] hyponatraemia, and rapidly advancing azotaemia, are angiotensin converting inhibitors likely to improve renal function.

Reduction in heart rate is to be expected with angiotensin converting enzyme inhibition in cardiac failure despite dilatation of resistance vessels and probably results from a combination of venous dilatation, reduced sympathetic tone,[16 45] and loss of the vagolytic effect of angiotensin II.[15 17] Although in the long term the reduction in blood pressure was generally well tolerated, initiation of treatment with captopril[54 55] or enalapril[56] may be associated with severe hypotension, bradycardia, and syncope. For this reason such treatment must be started under close supervision.

In response to the presumed reduction in preload and afterload[57 58] we observed a reduction in left ventricular dimensions. An improvement in systolic function is suggested by the improvement in the ratio of pre-ejection period to left ventricular ejection time which has been shown to correlate with left ventricular fraction.[28] The reduction in end diastolic dimension implies a reduction in filling pressure.

Apart from postural hypotension which caused symptoms in three patients, adverse reactions seemed to be no more common with enalapril than with placebo. Although very low ambulant pressures without symptoms seem to be tolerated by many patients, an excessive fall below renal autoregulatory thresholds may have accounted for the pronounced increase in serum creatinine associated with hypotension and hyponatraemia in one patient. The patient who developed diabetes did so at the end of the four months of study and had had raised fasting blood glucose concentrations before joining the study. Impaired glucose metabolism does not seem to be a feature of angiotensin converting enzyme inhibition,[59] however, in one study blood glucose concentration was not included in the coronary risk factors studied.[60]

Despite the minor consequent impairment of renal

function and occasional hypotension, angiotensin converting enzyme inhibitors clearly improve symptoms in heart failure. The reduction of ventricular arrhythmias moreover offers the distinct hope that these drugs may help to prolong survival in patients with cardiac failure.

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